REMARKS

This Amendment responds to the Office Action mailed on September 16, 2008. In the Office Action, the Examiner:

- rejected claim 58 under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement;
- rejected claims 49 and 57-61, 63 and 64 under 35 U.S.C. 112, first paragraph, as allegedly failing to reasonably provide enablement for a solvate;
- rejected claims 58 and 59 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention; and
- rejected claims 49 and 57-64 under 35 U.S.C. § 103(a) as being unpatentable over D'Amato (U.S. Patent No. 6,469,045) in view of Wolff, *M.E. Burger's Medicinal Chemistry 4th Ed. Part I*, Wiley: New York, 1979,336-337; in view of Bilodeau *et al.* (U.S. Patent Publication No. 2002/0137755), and in view of Kovesdi *et al.* (U.S. Patent Publication No. 2003/45498).

Claims 49 and 57-64 are pending. Claims 49 and 59 are amended by deleting the term "solvate." Claim 49 is also amended by substituting (1) the term "1-oxo-2-(2,6-dioxopiperidin-3-yl)-4-methylisoindoline" and its formula with the term "4-(amino)-2-(2,6-dioxo(3-piperidyl))-isoindoline-1,3-dione" and its formula; and (2) the words "in need thereof" with "having macular degeneration." The amendments are supported by the specification, for example, at page 15, lines 17-23; and at page 1, lines 16-20. Claim 58 is amended by deleting the words "a xanthine derivative." Claim 59 is also amended to correct a typographical error. Claim 60 is amended by substituting the words "antiangiogenesis compound" with "second active agent." No new matter is added by this Amendment.

The Applicant would like to express gratitude to the Examiner for the courtesy extended to the Applicant's attorney during a telephone interview, in which the patentability of the rejected claims in light of the cited references was discussed. But no agreement on patentability was reached. But the Examiner has agreed that the Applicant can change the compound 1-oxo-2-(2,6-dioxopiperidin-3-yl)-4-methylisoindoline" to "4-(amino)-2-(2,6-dioxo(3-piperidyl))-isoindoline-1,3-dione in this Amendment.

I. The Rejection of Claim 58 under 35 U.S.C. § 112 Should Be Withdrawn

On page 3 of the Office Action, the Examiner rejected claim 58 under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The Examiner alleged that the specific descriptions of a xanthine derivative is not defined by the instant specification and that the disclosure of the instant specification is not sufficient to support the use of a xanthine derivative as a second active agent. Solely to promote the allowance of the case and without acquiescing to the Examiner's rejection, claim 58 has been amended to delete the words "a xanthine derivative" and therefore, the rejection is moot.

In view of the above remarks, Applicant respectfully requests withdrawal of the rejection of claim 58 under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement.

II. The Rejection of Claims 49 and 57-61, 63 and 64 under 35 U.S.C. § 112, First Paragraph Should Be Withdrawn

On pages 3-9 of the Office Action, the Examiner rejected claims 49 and 57-61, 63 and 64 under 35 U.S.C. § 112, first paragraph as allegedly failing to reasonably provide enablement for a solvate while being enabling for a compound, or salts thereof. Applicant respectfully disagrees. Solely to promote the allowance of the case and without acquiescing to the Examiner's rejection, claims 49 and 59 are amended by deleting the term "solvate." Therefore, the rejection of claims 49 and 59 and their dependent claims is moot and should be withdrawn.

For the foregoing reasons, Applicant respectfully requests withdrawal of the rejection of claims 49 and 57-61, 63 and 64 under 35 U.S.C. § 112, first paragraph as allegedly failing to reasonably provide enablement.

III. The Rejection of Claims 58 and 59 under 35 U.S.C. § 112, Second Paragraph Should Be Withdrawn

On page 9 of the Office Action, the Examiner rejected claims 58 and 59 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The Examiner alleged that claim 58 is not clear about identifying a xanthine derivative as a second active agent in the composition for treating macular degeneration, and that the term derivative is allegedly not distinctly defined since it allegedly embraces indefinite number of compounds. Claim 58 is amended by deleting the words "a xanthine derivative." Therefore, the rejection of claim 58 is moot and should be withdrawn.

The Examiner also alleged that claim 59 is not clear about identifying a solvate of second active agent in the composition for treating macular degeneration. Claim 59 is amended by deleting the term "solvate." Therefore, the rejection of claim 59 is moot and should be withdrawn.

In view of the above remarks, Applicant respectfully requests withdrawal of the rejection of claims 58 and 59 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

IV. The Rejection of Claims 49 and 57-64 under 35 U.S.C. § 103(a) Should Be Withdrawn

On page 10 of the Office Action, the Examiner rejected claims 49 and 57-64 under 35 U.S.C. § 103(a) as being unpatentable over D'Amato (U.S. Patent No. 6,469,045) in view of Wolff, *M.E. Burger's Medicinal Chemistry 4th Ed. Part I*, Wiley: New York, 1979, 336-337; in view of Bilodeau *et al.* (U.S. Patent Publication No. 2002/0137755), and in view of Kovesdi *et al.* (U.S. Patent Publication No. 2003/45498). Applicant respectfully disagrees.

The current standard of obviousness takes into account of (1) whether there would have been a "reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed invention does;" and (2) whether the combination of elements would have yielded "predictable results" *i.e.*, whether there would have been a reasonable expectation of success. *See e.g., PharmaStem Therapeutics, Inc. v. ViaCell, Inc.*, 491 F.3d at 1342, 1360 (Fed. Cir. 2007) ("The burden falls on the patent challenger to show by clear and convincing evidence that a person of ordinary skill in the art would have had reason to attempt to make the composition or device, or carry out the claimed process, and would have had a reasonable expectation of success in doing so.") (emphasis added, internal quotations omitted).

It is alleged by the Examiner that the claims are obvious, because (1) D'Amato allegedly teaches a compound without a methyl group with the exact same core structure as claimed in the instant claims for inhibition of corneal neovascularization (macular degeneration); and (2) Wolff in Table 8.2 allegedly teaches that H and alkyl group in an aromatic ring of a compound are interchangeable and the compound possess the same property as evidence (*See* page 11 of the Office Action). This rejection is moot in view of the amendment of claim 49.

Claim 49 has been amended by substituting the term "1-oxo-2-(2,6-dioxopiperidin-3-yl)-4-methylisoindoline" and its formula with the term "4-(amino)-2-(2,6-dioxo(3-piperidyl))-isoindoline-1,3-dione" and its formula. The amended claim 49 does not recite a compound having a methyl or alkyl substitution in the isoindoline ring.

Further, the cited references, individually or in combination, fail to establish the obviousness of each limitation found in the claimed subject matter of the currently amended claims: the administration of the recited compound, 4-(amino)-2-(2,6-dioxo(3-piperidyl))-isoindoline-1,3-dione for the specific treatment of macular degeneration. *In re Ochiai*, 71 F.3d 1565, 1572. (Fed. Cir. 1995) (PTO must establish "that the invention as claimed in the application is obvious over cited prior art, based on the specific comparison of that prior art with claim limitations."). As discussed below, the Office also fails to meet the legal threshold for a finding of obviousness because the cited references would not have provided a reason to select the recited compound for the treatment of macular degeneration and would not have provided the legally required expectation of success.

Specifically, D'Amato does not provide a reason to specifically select the recited compound from the plethora of the compounds and general formula (Figures 1-5 and Columns 6-9). The Court held that it was not obvious to select one compound out of a prior art reference that disclosed a large number of compounds, in part, because "[r]ather than identify predictable solutions..., the prior art disclosed a broad selection of compounds any one of which could have been selected as a lead compound for further investigation." *Takeda,* 429 F.3d 1350 at 1360 (citing *In re Dillon*, 919 F.2d 688 at 692). The Court also held that "[a]bsent anything in the cited prior art suggesting which of the 10^{36} possible sequences corresponds to [a gene], the PTO has not met its burden of establishing that the prior art would have suggested the claimed sequences." *In re Baird*, 16 F.3d 380, 29 U.S.P.Q.2d 1550 (Fed. Cir. 1994). To establish a *prima facie* case of obviousness when a prior art reference

discloses a genus, the Office must show "[s]ome motivation to select the claimed species or subgenus [from] the prior art." ((MPEP §2144.08) (emphasis added). The PTO has failed to point out to any disclosure or suggestion in D'Amato that would motivate a skilled artisan to select the recited compound for treating macular degeneration.

Furthermore, Wolff merely discloses the dimethisoquin derivatives for anesthesia (page 337). Wolff does not teach or suggest the use of the recited compound, much less the treatment of macular degeneration. Absent any teaching or suggestion of the treatment of macular degeneration with the recited compound, one skilled in the art would not have had any reason to focus on the recited compound or its stereoisomers or salts and the treatment of macular degeneration, much less have an expectation of success. *See*, *e.g.*, *PharmaStem*, 491 F.3d at 1364. Indeed, Wolff teaches away from the claimed invention, because it only discloses dimethisoquin derivatives for anesthesia which has nothing to do with the claimed method. For purpose of obviousness analysis, a prior art that teaches away negates an obviousness rejection. "[A]n applicant may rebut a *prima facie* case of obviousness by showing that the prior art teaches away from the claimed invention in any material respect." *In re Peterson*, 315 F.3d 1325, 1331 (Fed. Cir. 2003). (Emphasis added.)

Therefore, D'Amato and Wolf, individually or in combination, do not render obvious the amended claims for treating macular degeneration with the recited compound.

Nonetheless, it is alleged that the claims are obvious, because Bildeau *et al.* allegedly teaches the use of therapeutically effective amount of several second compounds for diseases related to angiogenesis including macular degeneration and because Kovesdi *et al.* allegedly teaches the several intervention methods including surgical intervention as part of the treatment (*See* pages 12-13 of Office Action).

Bildeau *et al.* and Kovesdi *et al.* do not cure the defects of D'Amato and Wolff with respect to obviousness of the currenetly amended claims because they are silent about the use of the recited compound or its stereoisomers or salts. The Office has not pointed to any portion in Bildeau *et al.* and Kovesdi *et al.* that would have led one skilled in the art to use the recited compound for treating macular degeneration. In either Bildeau *et al.* or Kovesdi *et al.*, there is no teaching or suggestion that the recited compound is effective to treat macular degeneration. Thus, one of skill in the art would have had no reason to specifically select the recited compound within the instant claims. Further, the Patent Office

has not presented evidence to demonstrate that the recited compound of the claimed methods would be effective in treating macular degeneration. Without such evidence, no reasonable expectation of success exists because a reasonable expectation of success requires more than a motivation to simply "vary all parameters or try each of numerous possible choices until one possibly arrive[s] at a successful result...." *Medichem v. Robaldo*, 437 F.3d 1157, 1165 (Fed. Cir. 2006) (*quoting In re O'Farrell*, 853 F.2d 894, 903-04 (Fed. Cir. 1988); *see also KSR*, 127 S.Ct. at 1739 and 1742 (an obviousness determination takes into account whether the combination of elements would yield "anticipated success" or "predictable results"). Furthermore, the courts have long recognized the unpredictability of the biological properties of chemical compounds. *See, e.g., In re Eli Lilly & Co.*, 902 F.2d. 943, 948 (Fed. Cir. 1990) ("we recognize and give weight to the unpredictability of biological properties..."). None of the cited references teaches, suggests or discloses the method of treating macular degeneration with the recited compound. Without more specific guidance in the art, no reasonable expectation exists to use the recited compound of the instant methods for the treatment of macular degeneration. Thus, because the Patent Office has not presented sufficient evidence of a reasonable expectation of success, a *prima facie* case of obviousness has not been made. In view of the foregoing, Applicant respectfully requests withdrawal of the rejection of claims 49 and 57-64 under 35 U.S.C. § 103(a) as being unpatentable over D'Amato in view of Wolff; further in view of Bilodeau *et al.* and Kovesdi *et al.*

CONCLUSION

In light of the above amendments and remarks, Applicants respectfully request that the Examiner reconsider this application with a view towards allowance.

No fees in addition to the fee under 35 U.S.C. § 371 are believed due in connection with this Amendment. However, pursuant to 37 C.F.R. §1.136 (a)(3), the Commissioner is authorized to charge all required fees, fees under 37 C.F.R. §1.17 and all required extension of time fees, or credit any overpayment, to Jones Day Deposit Account No. 50-3013 (Attorney Docket No. 9516-314-999).

Respectfully submitted,

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/Kam W. Law/

Kam W. Law (Reg. No. 44,205)
For: Anthony M. Insogna (Reg. No. 35,203)
Jones Day
222 East 41st Street
New York, N.Y. 10017-6702
Tel: 212-326-3778